

Adrenal incidentaloma

Prevalence

5% post-mortem series

4% CT series

6-20% CT series in patients with Hx extra-adrenal malignancy

Commoner with increasing age

Associated with adrenal hyperfunction in 15%

Phaeochromocytoma (1-11% of AI) – tachycardia, high BP, flushing may be present but not necessarily. etc

Conn's syndrome – (1-3.3%) hypertension, hypokalaemia

Cushing's syndrome – central obesity, striae, High BP/Glu, Low K+

Androgen secreting tumours – rare, hirsutism, virilisation etc.

Non-functioning tumours in 85%

What are the chances of it being cancer?

<1% chance of being a met with no prior history of primary cancer

<5% chance of being a primary adrenal cancer

? chance of being a met with a known primary

Investigation and management focused on determining likelihood of functioning tumour and malignancy

Investigation

History and clinical examination suggesting functioning tumour

Biochemical testing

24 hour urinary catecholamines/metanephrines [Alternatively plasma free metanephrines: higher sensitivity (99%) cf. urinary catecholamines (86%) and metanephrines (77%); but difficult to get Lerner 2002]

Aldosterone-renin ratio. Good test for Conn's but aldosterone should be high normal or high (low renin with normal aldosterone gives elevated ARR in low-renin essential hypertension. Must stop beta-blockers (false-positives) and aldosterone antagonists (false negatives)

If ARR high, needs salt-loading test to confirm diagnosis because of significant daytime variation

Selective venous sampling recommended to localise tumour - 50%

concordance with CT over ?unilateral or bilateral Nwariaku 2006

Alternatively radiolabelled cholesterol (131-I iodocholesterol) scintigraphy, but poor uptake in small tumours

1mg dexamethasone overnight suppression test. 1mg DXM at 11pm, bloods at 8am. Using modern radioimmunoassay, most patients with normal adrenals do not produce cortisol. Therefore <138nmol/l = equivocal; >138nmol/l = autonomous glucocorticoid hypersecretion. AGH is called Cushing's if clinical features present or subclinical (SAGH) if no features SAGH seen almost exclusively in patients with adrenal incidentalomas 12.5% risk of developing Cushing's at 1 year.

Computed tomography

Risk of adrenal cancer related to size: 2% <2cm; 6% 4-6cm; **25% 6cm+**

Calcification, necrosis and haemorrhage rarely seen in benign tumours

Attenuation value <10HU 98% specific for benign adenomata (Singh 2008)

>50% washout of contrast medium after 10 mins has sn/sp of 95-98% for benign adenomata (Caoili 2002)

Controversial results suggesting MRI any better or worse than properly performed CT with 10 min washout

MRI does not rely on gadolinium washout, rather loss of signal after RF pulse. Fat loses signal rapidly.

PET scanning – may be useful in patients with known primary cancer.

Fine-needle aspiration cytology

Most commonly used in patients with AI and a history of extra-adrenal carcinoma. Typically in situations where PET unavailable. Largest series of 277 patients; sensitivity 81% (false negative 19%), specificity 99%.

Complication rate 2.8% (Welch 1994). NB. Phaeo must be excluded prior to FNAC to avoid hypertensive crisis.

Management strategies

Adrenalectomy for:

Functioning tumour

Non-functioning tumour > 6cm

Non-functioning tumour < 6 cm with calcification, haemorrhage or necrosis

Non-functioning tumour with positive PET or FNAC if solitary and appropriate in context of primary tumour

Follow-up for all others

Follow-up considerations

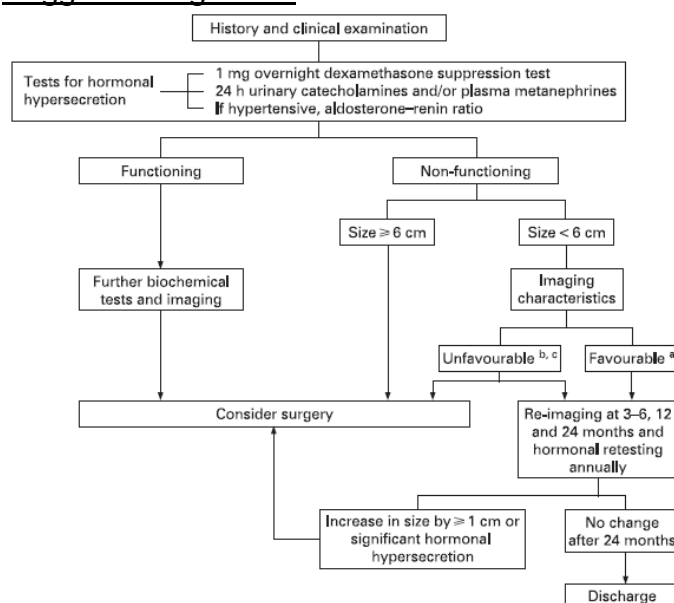
Non-functional to functional – 2-8% within 2 years (usually AI > 3cm)

Growth rate >1cm in 5-25% of incidentalomas. Of these 5% malignant when excised for increased growth alone.

No formal follow-up schedule validated.

Re-imaging at 6 months, 12 months and 24 months with repeat biochemical testing yearly

Suggested algorithm



Appendix

Anatomy

Adrenal 5 x 3 x 1 cm in length

Weight 5 g

Cortex from mesoderm; medulla from neuroectoderm

Cortex ~90% tissue; from out to in;

Zona glomerulosa mineralocorticoids (aldosterone)

Zona fasciculata glucocorticoids

Zona reticularis androgens and oestrogens

Cortex enlarged in fetus ? why

Medulla 10% tissue noradrenaline and adrenaline

Blood supply

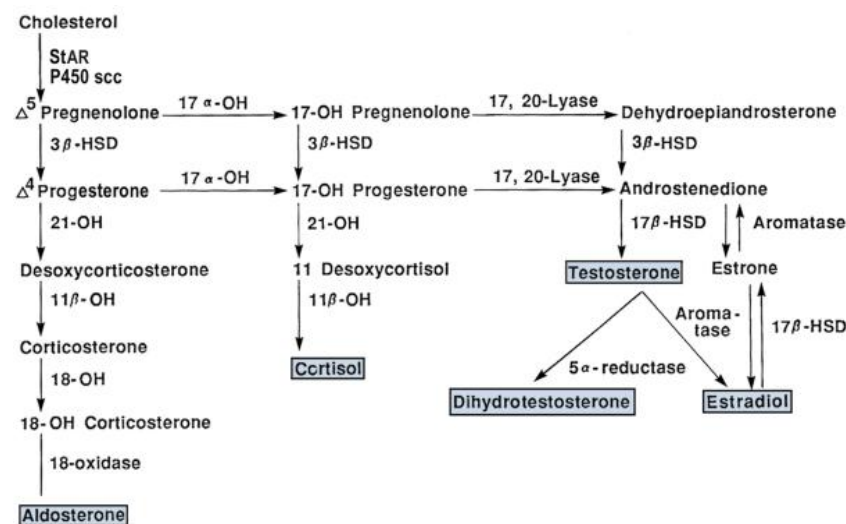
Arterial Main supply inferior phrenic

Additional branches from renal artery & aorta

Venous Right = common apical vein drains into IVC. Occasionally receives an aberrant unnamed hepatic branch vein

Left = common vein drains into renal vein opposite gonadal. Usually receives drainage from inferior phrenic coursing medially

Physiology



Major androgens DHEA, DHAE sulphate and androstenedione

Cortisol release regulated by hypothalamus-pituitary-adrenal axis via corticotrophin releasing hormone, producing ACTH from anterior pituitary

Cortisol release diurnal - peak at ~ 0600, trough at ~ midnight

Aldosterone release stimulated by angiotensin II (less important secondary response to low potassium – inhibits release)

Adrenal medulla hormones synthesised from phenylalanine in following order:

phenylalanine – tyrosine – L-Dopa – dopamine – noradrenaline – adrenaline

Dopamine, NA and Adr considered catecholamines, others precursors. NA

comprises ~70% total stored catecholamines (15% each for others)

Half-life catecholamines ~20s; broken down by MAO and catechol

methyltransferase; largest metabolite urinary VMA

Selected adrenal disorders

(i) Cushing's syndrome

Central obesity, moon face, thin skin, bruising, striae, hirsutism, hypertension, diabetes etc.

Causes

Endogeneous (steroid administration commonest cause)

Endogenous

Pituitary tumours (Cushing's syndrome)*	68%
Ectopic ACTH production*	12%
Adrenal adenoma	10%
Adrenal carcinoma	8%

* ACTH dependent. Lung cancer accounts for > 50% ectopic ACTH production (invariably due to tumour)

Diagnosis

Blood sampling

1. 24 hour cortisol secretion on 3 occasions most reliable estimate of cortisol secretion
2. Midnight ACTH-cortisol measurement on 2 occasions – determines whether ACTH dependent (pituitary/ectopic) or ACTH independent (adrenal)
3. High dose DXM suppression test (2mg qds 2 days – measure plasma cortisol) – distinguishes pituitary from ectopic ACTH.

Radiographic imaging (adrenal/pituitary)

Adrenal tumours >5cm, calcification, necrosis
haemorrhage suggestive of carcinoma vs adenoma
High signal intensity on T2 weighted images also highly suggestive of malignancy

Management

Pituitary disease

Transphenoidal hypophysectomy
Radiation for surgery failures

Ectopic production

Treat primary tumour

(ii) Adrenocortical carcinoma

Even after surgical removal differentiating benign from malignant adrenal lesions may be difficult – Weiss criteria designed to assist pathologists

- High mitotic rate (>5 per 50 high-power field)
- Atypical mitoses
- Venous invasion
- High nuclear grade (Fuhrman 3-4)
- Absence of cells with clear cytoplasm (<25% of cells)
- A diffuse growth pattern (more than one third of tumor)
- Necrosis
- Sinusoidal invasion
- Capsular invasion

Three or more are needed for diagnosis of carcinoma.

Carcinoma

Non-functional in 40%; functional in 60% (of these 60% Cushing's syndrome)

With exception of rare testosterone-secreting tumours, highly malignant with 5YS ~35%. Early metastasis to lungs, liver, lymph nodes common; local invasion typical

Rx = **surgical extirpation** – improved survival with complete excision

Radiotherapy only for palliation; chemoresistant (p-glycoprotein)

(iii) Conn's syndrome (primary hyperaldosteronism)

1-2% of hypertensive patients

Adenoma >> carcinoma

Hypertension, hypernatraemia, hypokalaemia and alkalosis

Oedema not a feature due to 'mineralocorticoid escape'

Hypertension, low plasma renin activity (PRA) and high aldosterone hallmarks of diagnosis (differentiates secondary from primary aldosteronism)

Diagnosis with ARR (see above) – confirm with salt loading test and postural stimulation test. Lateralisation using CT +/- adrenal vein sampling

Management

Idiopathic hyperaldosteronism	medical with spironolactone or amiloride
Autonomous focus	adrenalectomy

(iv) Multiple endocrine neoplasia

MEN 1	Autosomal dominant defect MEN 1 gene chromosome 11 Pituitary, parathyroid hyperplasia and pancreatic tumours
MEN 2a	Parathyroid hyperplasia, medullary C-cell thyroid carcinoma, pheochromocytoma
2b	Medullary C-cell thyroid carcinoma, pheochromocytoma, marfanoid, neurofibromas